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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Aerosol Delivery of Midazolam

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AEROSOL DELIVERY OF MIDAZOLAM

DESCRIPTION

BACKGROUND OF THE INVENTION

Field of the Invention

The invention is directed to the aerosolized delivery of midazolam to a patient's nasal or lung mucosa.

Description of the Prior Art

8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazol[1,5-a][1,4]benzodiazepine, which is better known as "midazolam", is a hypnotic-sedative drug with anxiolytic and marked amnestic properties. Midazolam provides the patient with a "calming" effect, and causes brief anterograde amnesia, thus making the drug useful in conjunction with regional anesthesia and as a sedative for short operative procedures such as gastroscopy, cystoscopy, endoscopy, dentistry, cardiac catheterization, etc. Recent discoveries in cardiorespiratory stability following administration have suggested that midazolam will be useful for anesthetic induction in poor-risk, elderly, and cardiac patients. The basic pharmacology of midazolam is similar to other benzodiazepines such as diazepam; however, most investigations have shown midazolam is more potent than diazepam and produced more complete anterograde amnesia.

Midazolam, in its base form, is a white to yellow crystalline compound which is insoluble in water. However, the imidazole ring is relatively basic and allows the preparation of salts which are stable in water solution. A typical example of an aqueous midazolam salt formulation is VERSED®, which is midazolam hydrochloride available from Roche Laboratories. Water solubility is achieved by adding hydrochloric acid to achieve a pH below 4. At pH 4 or lower, the drug has an open benzepine ring which imparts water solubility. Midazolam is typically provided to patients via intramuscular injection or by the intravenous route. Water solubility of midazolam has been shown to reduce pain on injection and venous thrombosis compared with diazepam administered in organic solvents.

Recently, experiments with the nasal administration of midazolam have shown that the nasal route is useful in rapidly sedating children prior to the induction of anesthesia (see Niall et al., "Preanesthetic Sedation of Preschool Children Using Intranasal Midazolam", *Anesthesiology*, 69:972-974, December 1988, and Karl et al., "Comparison of the Safety and Efficacy of Intranasal Midazolam of Sufentanil for Prinduction of Anesthesia in Pediatric Patients", *Anesthesiology*, 76:209-215, February 1992). Walbarg et al., "Plasma Concentrations of Midazolam in Children Following Intranasal Administration", *Anesthesiology*, 74:233-235, February 1991, have shown that intranasal administration of midazolam rapidly achieves sedative plasma concentrations in

children. Induction of anesthesia in pediatric patients is a challenge to anesthesiologists and any improvement in delivery technique would be beneficial for avoiding potentially hazardous psychological and physiological sequelae. Transmucosal delivery of midazolam is currently performed simply by drawing the water solubized compound into a syringe and squirting it into a patient's nose or mixing it with a flavoring agent and placing it sublingually. The intranasal administration of midazolam has the advantages of ease of administration and avoidance of painful injections. However, intranasal administration of midazolam is complicated by stinging, due to the presence of acid in the formulation which is required to make the drug water soluble. In addition, the VERSED® preparation has a bitter taste which is difficult to mask with flavoring agents and sweeteners.

SUMMARY OF THE INVENTION

It is an object of this invention to provide an improved delivery method for midazolam.

It is another object of this invention to provide a metered dose inhaler formulation of midazolam suitable for intranasal delivery or delivery to the lungs.

According to the invention, midazolam is provided in its lipid-soluble, water-insoluble, free base form to the nasal or lung mucosa via an aerosol spray. The propellant can be any of the well-recognized freons or freon combinations

traditionally used in metered dose inhalers; however, due to the growing concern about ozone depletion and the world-wide treaties requiring the phase out of freons and halons, the propellant is preferably 1,1,1,2-tetrafluoroethane (HFC-134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFC-227) or some other hydrofluorocarbon or non-ozone depleting substance. The midazolam base is solubilized in the propellant using a suitable solvent. In the case of HFC-134a and HFC-227 propellants, the solvent can be ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, and dimethoxy ethane.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

Midazolam base is freely lipid soluble. In order to cross any physiological membrane, a drug must be in a non-ionized lipid soluble state. This invention is directed to the use of midazolam in its base form being administered via aerosolized spray to the transmucosal membranes. The base form of midazolam will cross the nasal or oral mucosa freely at physiological pH. For example, the nasal pH is typically between pH 5.5 and pH 6.6. Midazolam is lipid soluble within the nasal pH range and, when dissolved in a minimal amount of excipient, will be rapidly and extensively adsorbed through the nasal mucosa.

Midazolam is insoluble in water at physiological pH, and thus not suitable for use in

an aqueous suspension.

In this invention, midazolam is provided to the patient in aerosolized form utilizing a metered dose inhaler (MDI) for delivery of the compound to the nasal or oral cavity. MDIs have been used extensively for the treatment of respiratory disorders such as asthma as well as other diseases and have proven to be an effective means to produce a reproducible preselected dose of medicament in a predictable spray pattern and droplet size. The object of aerosolized medication delivery is to provide the medicament in a stable suspension or solution form in a propellant with minimal additives at a suitable concentration to achieve a clinical effect. Effective MDI formulations will have a predictable droplet size that is a function of many factors including the relative volumes of the drug, co-solvents and propellant, and the density, shape, and hygroscopicity of the particles. The inventor has determined the MDI is an ideal delivery device for midazolam since it will allow a precise quantity of the midazolam base to be deposited uniformly on the nasal or oral mucosa for rapid absorption. Thus, the invention provides an effective, less painful method for providing midazolam compared to injection or administration of a low pH solution to the nose. The MDI, by design, only allows a precise quantity of drug to be delivered, hence the dangerous clinical side effects which can result with overdosage of midazolam can be avoided.

Traditional MDI technology utilizes freon or chlorofluorocarbon propellants. All chlorine

containing halohydrocarbons have been implicated in the destruction of the earth's ozone layer with subsequent adverse side effects to human and animal life. As such, the Montreal Protocol has been signed by a majority of the world's industrial nations and prescribes the phase out of freons by 1996. In view of this, the use of freon gases for delivery of the midazolam base is not recommended.

Currently, the two best alternative propellants to freons are HFC-134a and HFC-227. These substances have zero ozone depletion potential and toxicological data packages being assembled by international consortia suggest that they are safe for human use. As such, it is preferable that HFC-134a or HFC-227 or a combination of the two propellants be used within the practice of this invention.

A significant problem with HFC-134a and HFC-227 is that they have poor solubility characteristics compared to freon substances. However, the solubility problem has been overcome in the present invention by the discovery that midazolam base can be solubilized in either HFC-134a or HFC-227 or a blend of HFC-134a and HFC-227 by first dissolving the midazolam base in a suitable solvent such as ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, or dimethoxy ethane, and then combining the solution of the midazolam base and solvent together with HFC-134a or HFC-227. The pH of the solution is preferably in the physiological range of pH 5 to pH 8.

A suitable MDI formulation should comprise 1-40% w/w midazolam base, 50-98% propellant (preferably 134a or 227, or a combination thereof), and 1-30% of a solvent. When HFC-134a or HFC-227 is used as the propellant, the solvent is preferably ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, or dimethoxy ethane. The formulation should be kept under pressure in a MDI cannister that delivers approximately 25-100 microliters per dose including about 0.5-2mg of midazol per dose depending on the needs of the patient.

In view of the practical results which can be obtained by aerosolized delivery of the base form of midazolam, it is suggested that the same advantages can be realized with other benzodiazepines and benzodiazopine antagonists including in particular diazepam, lorazepam, clonazepam, flurozepam, triazepam, temazepam, and chlordiazepoxide as exemplary benzodiazapines and fluomiazenic as an exemplary benzodiazepine antagonist. As discussed above, the benzodiazepine or benzodiazopine antagonists would first be dissolved in their base form at physiologic pH (pH5 to pH8). Then, the solution would be combined with a suitable propellant such as HFC-134a or HFC-227. The concentrations of components in the MDI formulation and dosages delivered from the MDI canister would be the same as or comparable to those described above for the midazolam MDI formulation.

While the invention has been described in terms of its preferred embodiments, those skilled in the art will recognize that the invention can be practiced with modification within the spirit and scope of the appended claims.

CLAIMS

We claim:

1. A method for providing midazolam to a patient, comprising the steps of:

generating an aerosol spray which includes a single dose of midazolam in base form and a propellant; and

delivering said aerosol spray to a patient's nasal or lung mucosa.

2. The method of claim 1 wherein said step of generating an aerosol spray is achieved using a metered dose inhaler which includes

50-98% w/w of said propellant;

1-30% w/w of a solvent capable of disolving midazolam in said propellant; and

1-40% w/w of midazolam in its base form.

3. The method of claim 2 wherein said propellant is selected from the group consisting of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane, and wherein said solvent is selected from the group consisting of ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, and dimethoxy ethane.

4. A metered dose inhaler formulation, comprising:

50-98% w/w of said propellant;

1-30% w/w of a solvent capable of disolving midazolam in said propellant; and

1-40% w/w of midazolam in its base form.

5. The metered dose inhaler formulation of claim 4 wherein said propellant includes at least one compound selected from the group consisting of 1,1,1,2-tetrafluorethane and 1,1,1,2,3,3,3-heptafluoropropane.

6. The metered dose inhaler formulation of claim 4 wherein said solvent is selected from the group consisting of ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, and dimethoxy ethane.

7. A method of preparing an MDI formulation comprising midazolam in its base form and at least one propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane, comprising the steps of:

dissolving midazolam in its base form in a solvent selected from the group consisting of ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, and dimethoxy ethane to form a solution; and then

combining said solution with at least one propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane to produce an MDI formulation, said MDI formulation including 50-98% w/w of said propellant, 1-30% w/w of said solvent, and 1-40% w/w of midazolam in its base form.

8. A method for providing a benzodiazopine or benzodiazopine antagonist to a patient, comprising the steps of:

generating an aerosol spray which includes a single dose of a drug selected from the group consisting of benzodiazopines and benzodiazopine antagonists, said drug being present in base form, and a propellant; and

delivering said aerosol spray to a patient's nasal or lung mucosa.

9. The method of claim 8 wherein said drug is selected from the group consisting of midazolam, diazepam, lorazepam, clonazepam, flurazepam, triazepam, temazepam, fluomazenic and chlordiazepoxide.

10. A method of preparing an MDI formulation comprising a drug in its base form selected from the group consisting of benzodiazopines and benzodiazopine antagonists and at least one propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane, comprising the steps of:

dissolving said drug in its base form in a solvent selected from the group consisting of ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, and dimethoxy ethane to form a solution; and then

combining said solution with at least one propellant selected from the group consisting of

1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane to produce an MDI formulation, said MDI formulation including 50-98% w/w of said propellant, 1-30% w/w of said solvent, and 1-40% w/w of said drug in its base form.

11. A metered dose inhaler formulation, comprising:

50-98% w/w of said propellant;

1-30% w/w of a solvent capable of disolving benzodiazopines and benzodiazopine antagonists in said propellant; and

1-40% w/w of a drug in its base form selected from the group consisting of benzodiazopines and benzodiazopine antagonists.

12. The metered dose inhaler formulation recited in claim 11 wherein said drug is selected from the group consisting of midazolam, diazepam, lorazepam, clonazepam, flurazepam, triazepam, temazepam, fluomazenic and chlordiazepoxide.

ABSTRACT OF THE DISCLOSURE

Midazolam, a short acting central nervous system depressant, is delivered to a patient as an aerosol spray in its base form. Preferably, midazolam is provided via a metered dose inhaler formulation which includes non-ozone depleting propellants such as 1,1,1,2-tetrafluorethane, and 1,1,1,2,3,3,3-heptapfluoropropane, together with solvents selected from the group consisting of ethyl alcohol, α-tocopherol, α-tocopherol acetate, polypropylene glycol, polyethylene glycol, lactate, diethyl ether, and dimethoxy ethane.